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Synthesis and Antimicrobial Activity of Pyrimidine

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ABSTRACT

1-amino-6-(furan-2-yl)-4-methylpyrimidine-2(1H)-thione (1) on reaction with acyl chloride (a-c) yieldsN-(6-(furan-2-yl)-4-methyl-2-thioxopyrimidin-1(2H)-yl)alkyl amide (2).The fusion of compound (2) with hydrazine hydrate yields 3-alkylethyl-6-(furan-2-yl)-8-methyl-9aH-pyrimido[1,2-b][1,2,4,5]tetrazine(3a-c). The structures of all the compounds series (2a-c) and (3a-c) were characterized analytically. The compounds were also monitored for anti microbial activity.

Introduction

In recent years lots of research was done to synthesis anti-microbial actives compounds for various microorganisms, particularly for bacteria and several fungi. The numerous derivatives of pyrimidine heterocycle moiety and natural products have been synthesized for their antibacterial, Insecticidal, anti-HIV, antifungal,anticancer and anti-inflammatory activities.[1-7]

On the other hand, tetrazole were reported with their anticancer, antiparasitic, antibacterial, antifungal agents and antifolate activity.[8-12]

Hence,pyrimidine and tetrazole containing compounds into one molecule may have good medicinal property. Thus it was thought to explore this type of merge molecules. The present communication deals with the synthetic approach shown in scheme-1.

Experimental

Materials and Methods

Furanylacetone was procured from Sigma Aldrich.All other reagents were used laboratory grade.

The IR spectra of all compounds were taken in KBr pellets on a Nicolet 400D spectrometer. Proton NMR spectra were recorded on a Bruker (400 MHz) spectrometer. Deutorated DMSO was used as a solvent. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. All the compounds were checked for their purity by TLC. The characterization data of all these compounds are given in Table.1.

The antibacterial activity of both the series of compounds were studied against gram +Ve and –Ve bacteria shown in Table-2. The activity was measured at a conc, 50µg/ml by agar-cup plate method. [13] The % age inhibition of growth of bacteria by the compounds is shown in Table-2.

The antifungal activity of both the series of compounds were measured at 1000ppm concentration in vitro Plant pathogen shown in Table-3 have been selected for study.[14]

Synthesis of 1-amino-6-(furan-2-yl)-4-methyl pyrimidine-2(1H)-thione (1)

The furanylacetone (0.01 mole) reflux with thio-semicarbazide in presence of ethanol containing with catalytic amounts of piperidine for 4-5hrs. Then cool the reaction mixture and pour in it ice, solid product formed. Filter, washed with cold water and dried it. The yield of the product was 82 % and the product melts at 197-198^{o}C.For $C_9H_9N_3OS$(207) Calcd.: %C,52.16; %H,4.38; %N,20.27; %S,15.47.Found: %C,52.1; %H,4.3; %N,20.2; %S,15.4. IR(KBr)(cm^{-1}):3361(NH2), 3080 (Aromatic C-H stretch), 2848(C-H), 760(Aromatic C-H bending), 1620-1580 (Aromatic C-C stretch), 1650(C=N), 1216 (C=S),1050(C-O-C).^{1}HNMR:8.65(s,1H,Pyrimidine-H),8.20-7.30(m,4H,Ar-H), 5.70 (s,2H,NH_2) and 2.35 (s,3H, CH_3).

Synthesisof N-(6-(furan-2-yl)-4-methyl-2-thioxopyrimidin-1(2H)-yl)alkylamide (2)

Treatment of 1-amino-6-(furan-2-yl)-4-methylpyrimidi ne-2(1H)-thione (1) with acyl chloride in pyridine was reflux for 6-7 hrs. Then reaction mixture was cooled under tap water, then poured into cold H_2O. The solid product which precipi -tated was collected by filtration, washed with solid product with water, dried and crystallized from ethyl alcohol. The details are given in Table-1.

Synthesis of 3-alkylethyl-6-(furan-2-yl)-8-methyl-9aH-pyrimido[1,2-b][1,2,4,5] tetrazine (3a-c)

Compounds N-(6-(furan-2-yl)-4-methyl-2-thioxopyrimidin-1(2H)-yl) alkyl amide (2) fusion with hydrazine hydrate to yielded 3-alkylethyl-6-(furan-2-yl)-8-methyl-9aH-pyrimido [1,2-b] [1,2,4,5] tetrazine (3a-c).Then reaction mixture wascooled under tap water, then poured into cold H2O. The solid product which precipitated was collected by filtration,washed with solid product with water, dried and crystallized from ethyl alcohol.

The details are given in Table-1.

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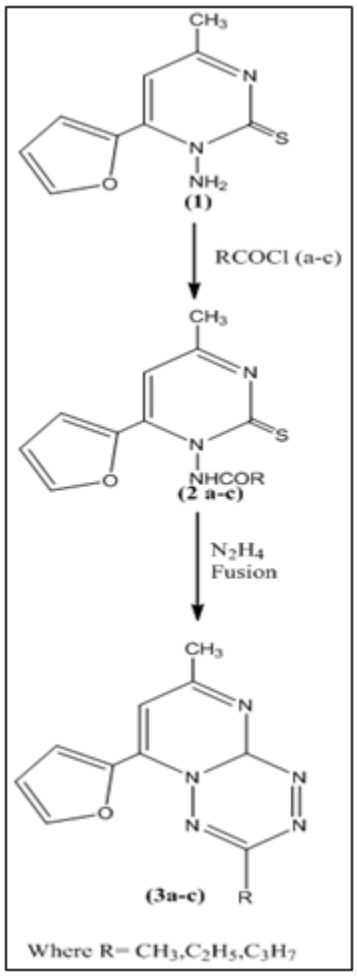

(Scheme-1)

Results and discussions

The furanylacetone(0.01 mole) on reaction with thio-semicarbazide in presence of ethanol gives 1- amino-6-(furan-2-yl)-4-methylpyrimidine-2(1H)-thione (1). Its IR spectrum revealed absorption bands due to NH2,C=N and C=S groups near 3361, 3308, 1644 and 1216 cm^{-1}, respectively. The 1H NMR spectrum revealed (CH3) protons as a singlet signal around 2.35 ppm, singlet at 5.70 ppm assigned to the NH_2 protons, singlet at 8.65 ppm assigned to the H-5 pyrimidine ring and multiplet at 7.30–8.20 ppm assigned to the aromatic protons.

Table 1. Physical and Analytical Data of the Compounds

Comp. No.	Molecular Formula	M.P. * ˚C	Elemental Analysis			
			C%	H%	N%	S%
			Calcd. (Found)	Calcd. (Found)	Calcd. (Found)	Calcd. (Found)
2a	$C_{11}H_{11}N_3O_2S$ (249)	235 -236	53.00 (52.9)	4.45 (4.4)	16.86 (16.8)	12.86 (12.8)
2b	$C_{12}H_{13}N_3O_2S$ (263)	242 -243	54.74 (54.7)	4.98 (4.9)	15.96 (15.9)	12.18 (12.1)
2c	$C_{13}H_{15}N_3O_2S$ (277)	247 -248	56.30 (56.2)	5.45 (5.4)	15.15 (15.1)	11.56 (11.5)
3a	$C_{11}H_{11}N_5O$ (229)	218 -219	57.63 (57.6)	4.84 (4.8)	30.55 (30.5)	-
3b	$C_{12}H_{13}N_5O$ (243)	223 -224	59.25 (59.2)	5.39 (5.3)	28.79 (28.7)	-
3c	$C_{13}H_{15}N_5O$ (257)	212 -213	60.69 (60.6)	5.88 (5.8)	27.22 (27.2)	-

Treatment of 1-amino-6-(furan-2-yl)-4-methyl pyrimidine -2(1H)-thione (1) with acyl chloride yielded N-(6-(furan-2-yl)-4-methyl-2-thioxopyrimidin-1(2H)-yl)alkylamide(2a-c). The IR spectrum of compound 2c showed a strong band in the region of 1695 cm-1 characteristic of C=O of secondary amide. The two bands in the region of 3190, 3320 cm-1 are the stretching modes of HNCO and N=C–OH groups. The 1H NMR of 2c showed a singlet at d 9.98, 10.76 ppm (1H, HNC=O or N=C–OH) and a singlet at d 11.33 ppm (1H, HNCOCH3).

Compounds N-(6-(furan-2-yl)-4-methyl-2-thioxopyrimidin-1 (2H)-yl)alkylamide (2a-c) fusion with hydrazine hydrate to yielded 3-alkylethyl-6-(furan-2-yl)-8-methyl-9aH–pyrimido [1,2-b] [1,2,4,5] tetrazine (3a-c). The IR spectrum exhibited the absence of band at 1695 cm-1 of C=O and the presence of NH band at 3329 cm-1. 1H NMR showed signal at d 12.38 ppm for NH tetrazine ring. The C, H, N analysis data of all compounds are presented in Table-1.

Table 2. Antibacterial Activity of Compounds (2a-c) and (3a-c)

Comp. No.	Zone of Inhibition(mm)			
	Gram +ve		Gram -ve	
	Bacillus Subtilis	Staphylococcus aureus	Kllebsiella promioe	E.coil
2a	55	49	63	61
2b	72	51	82	69
2c	70	47	80	63
3a	59	49	74	62
3b	60	44	60	59
3c	70	50	81	66
Tetracycline	79	55	87	72

All the elemental and spectral features suggest that the data are consistent with the predicted structure shown in Scheme-1. The LC-MS of selected compounds shows the peak of M^+ ion which is consistent of their molecular weight. All these facts confirm the structures (2a-c) and (3a-c).

Table 3. Antifungal Activity of Compounds (2a-c) and (3a-c)

Comp. No.	Zone of Inhibition at 1000 ppm (%)			
	Botrydepladia Thiobromine	Nigrosspora Sp.	Penicillium Expansum	Rhizopus Nigricuns
2a	58	66	57	55
2b	68	74	72	67
2c	62	68	64	62
3a	60	70	66	59
3b	61	69	65	61
3c	75	72	70	64

The examination of antibacterial activity data reveals that all compounds toxic against microbes and the compounds **2b** and **3b** found more active against the gram-positive and gram-negative bacteria.

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